

CASE REPORT

INTERMEDIATE

CLINICAL CASE

Quadruple Bioprosthetic Valve Replacement in a Patient With Severe Carcinoid Heart Disease



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ABSTRACT

Carcinoid heart disease typically affects the tricuspid and pulmonary valves, causing severe regurgitation and/or stenosis. Valve surgery has been shown to reduce right heart failure and improve long-term prognosis in these patients. We report a severe case of a patient with all 4 heart valves involved who underwent successful quadruple bioprosthetic valve replacement. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:271-6)

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Carcinoid heart disease (CaHD) is a valvular complication of metastatic neuroendocrine tumors (NET) and usually involves the tricuspid and pulmonary valves. The left-sided heart valves are rarely involved but may be affected in the presence of a persistent foramen ovale (PFO). Valve surgery in CaHD patients has been shown to reduce progressive right heart failure that may otherwise have a worse outcome than the oncological

prognosis. This report describes the case of a patient with severe CaHD affecting all 4 valves who underwent quadruple bioprosthetic valve replacement successfully.

CASE

A 70-year-old male patient was referred to the authors' center from another hospital with a history of smoking, insulin-dependent diabetes mellitus type 2, and moderate renal failure (glomerular filtration rate of 38 ml/min/1.73 m²).

MEDICAL HISTORY. The patient first presented with congestive heart failure 6 months earlier and was diagnosed using abdominal computed tomography and gallium-68-labeled (DOTA⁰-Phe¹-Tyr³)octreotide (⁶⁸Ga-DOTATOC) positron emission tomography-computed tomography with a small intestinal NET and metastases to the liver as well as mesenteric and retroperitoneal lymph nodes. Further cardiac assessment revealed CaHD with severe involvement of all 4 heart valves. Interestingly, the patient's younger sister, still alive, had a small intestinal NET with

LEARNING OBJECTIVES

- To understand the pathophysiology and clinical presentation of patients with severe carcinoid heart disease and typical findings on echocardiography.
- To understand aspects of surgical therapy for carcinoid heart disease and acknowledge that some patients can benefit from replacement of all 4 valves in the same procedure.
- These patients are best treated through multidisciplinary collaboration.

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Informed consent was obtained for this case.

Manuscript received September 2, 2019; revised manuscript received November 1, 2019, accepted November 2, 2019.

**ABBREVIATIONS
AND ACRONYMS****CaHD** = carcinoid heart disease**LMW** = low molecular weight**NET** = neuroendocrine tumor**PFO** = persistent foramen
ovale**TTE** = transthoracic
echocardiography

CaHD and had undergone replacement of the tricuspid and pulmonary valves 12 years earlier.

About 12 months before surgery, the patient began to be affected by flushes, which subsequently improved with long-acting somatostatin analog therapy (octreotide long-acting release, 30 mg every fourth week). He experienced a general weight loss of 25 kg, despite having severe leg edema, which required high doses of oral and intravenous diuretics. The patient experienced dyspnea on light exertion and general fatigue. Upon presentation at the authors' hospital, he had moderate pitting edema of the lower legs, a regular cardiac rhythm, and a clear systolic murmur over the apex. Blood pressure was 130/55 mm Hg. Relevant laboratory findings were as follows: hemoglobin, 111 g/l; N-terminal pro-B-type natriuretic peptide (NT-proBNP), 2,390 ng/l; creatinine, 154 µmol/l; 24-h urinary 5-hydroxyindole acetic acid (urine [U] 5-HIAA test), 215 µmol/day; and chromogranin A, 62 nmol/l.

INVESTIGATIONS. On transthoracic echocardiography, all 4 valves were fibrotic with moderate to severe regurgitation (Table 1, Figures 1 to 4). The left ventricle had normal dimensions with a systolic ejection fraction of 50%. The right ventricle was dilated with mildly reduced systolic function and a tricuspid annular plane systolic excursion of 2.5 cm. There was no evidence of a PFO or other intracardiac shunt. Coronary angiography showed no significant coronary stenoses.

DIFFERENTIAL DIAGNOSIS. The symptoms and findings were typical of severe CaHD, which is one of a few systemic diseases with possible manifestations in all 4 heart valves simultaneously, others being infective endocarditis and rheumatic heart disease.

MANAGEMENT. After evaluation by a multidisciplinary team, the patient was found to have indications for quadruple valve replacement, and he was assessed to be in operable condition. His oncological situation was stable with an unchanged

radiological tumor burden and steady levels of (U) 5-HIAA and chromogranin A. The initial part of the operation was uneventful without flushing or hypotension, and an intravenous octreotide infusion was given throughout the procedure. On-table transesophageal echocardiography reconfirmed the valvular pathology previously described (Videos 1, 2, and 3). The patient's surgery was undertaken through a median sternotomy with cannulation of the ascending aorta and both venae cavae. Cold blood cardioplegia was administered every 20 minutes of aortic cross-clamping in an antegrade fashion and in large amounts for optimal protection of the right ventricle. Intraoperative findings were consistent with the preoperative diagnosis, and all diseased valves were excised before being replaced with bioprostheses, except for the tricuspid valve in which the prosthesis was implanted with the native valve left in place. The sequence of valve replacement was mitral-aortic-pulmonary-tricuspid. To enhance flow conditions when closing the incision over the pulmonary valve prosthesis, a wide pericardial patch was used for right ventricular outflow tract enlargement. Finally, an epicardial permanent pacing wire was attached to the right ventricle, in the event of a permanent atrioventricular block.

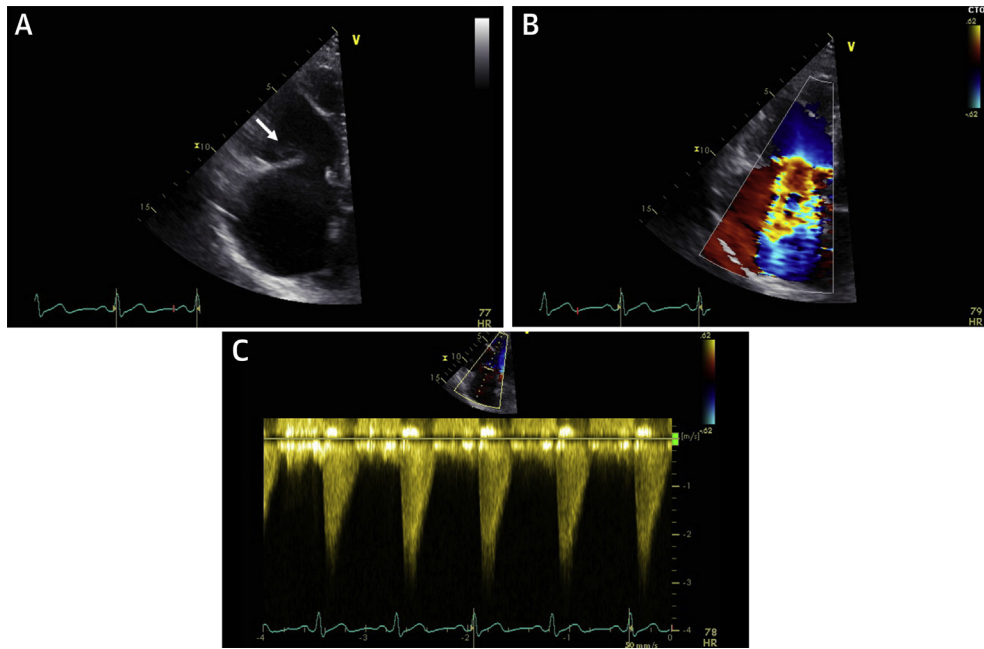
The postoperative course was uneventful; the patient was in sinus rhythm with no evidence of right ventricular failure. There was no significant infection or need for dialysis. He was given intravenous octreotide for 3 days in the intensive care unit and was able to be discharged from the hospital on day 10. Chest radiography showed no pleural effusion or signs of congestive heart failure (Figure 5). However, he was readmitted 4 days later with spontaneous retroperitoneal bleeding from the right psoas muscle, which healed without intervention after changing warfarin therapy to low-molecular-weight (LMW) heparin. Histological analyses of the excised valve components were consistent with CaHD.

FOLLOW-UP. Nine months after the procedure, the patient was in New York Heart Association (NYHA) functional class II without leg edema and exercising

TABLE 1 Characteristics of Diseased Heart Valves and Type of Implanted Bioprosthetic Valve

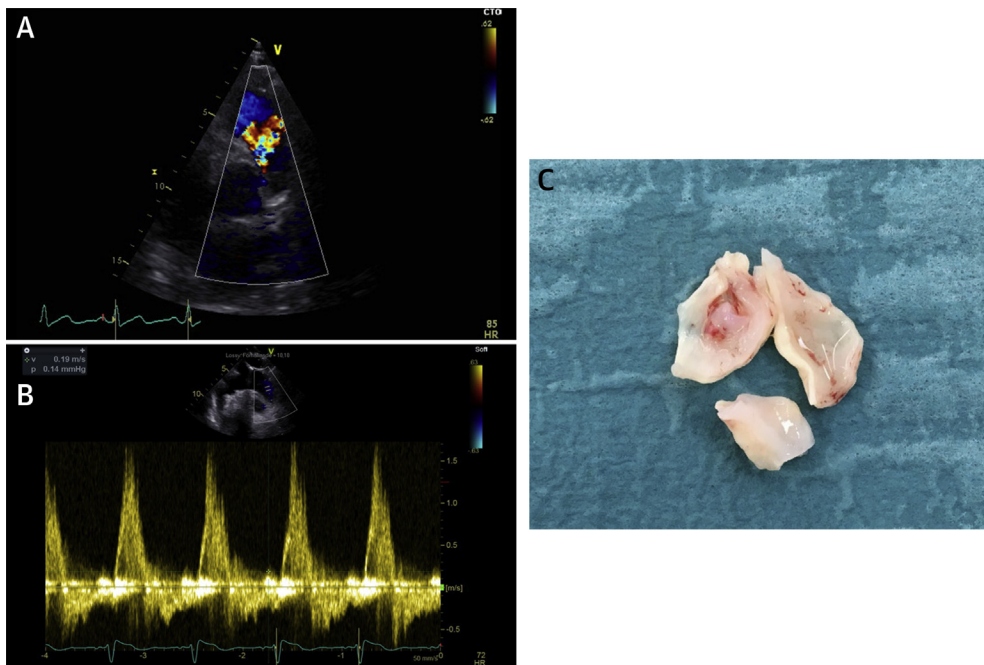
Valve Position	Valve Dysfunction on Echocardiography	Intraoperative Findings	Figure	Bioprosthetic Valve
Tricuspid	Severe regurgitation	Severely fibrotic, shortened chordae, retracted into right ventricle		Carpentier-Edwards Perimount Plus 27 mm
Pulmonary	Moderate regurgitation	Fibrotic, stiff cusps	Figure 2C	Carpentier-Edwards Perimount Magna-Ease 23 mm
Aortic	Moderate to severe regurgitation	Tricuspid, fibrotic cusps, retracted free edges	Figure 3C	Carpentier-Edwards Perimount Magna-Ease 23 mm
Mitral	Severe regurgitation	Severely fibrotic, retracted, fusion and shortening of chordae	Figure 4D	Carpentier-Edwards Perimount Plus 27 mm

FIGURE 1 Tricuspid Valve

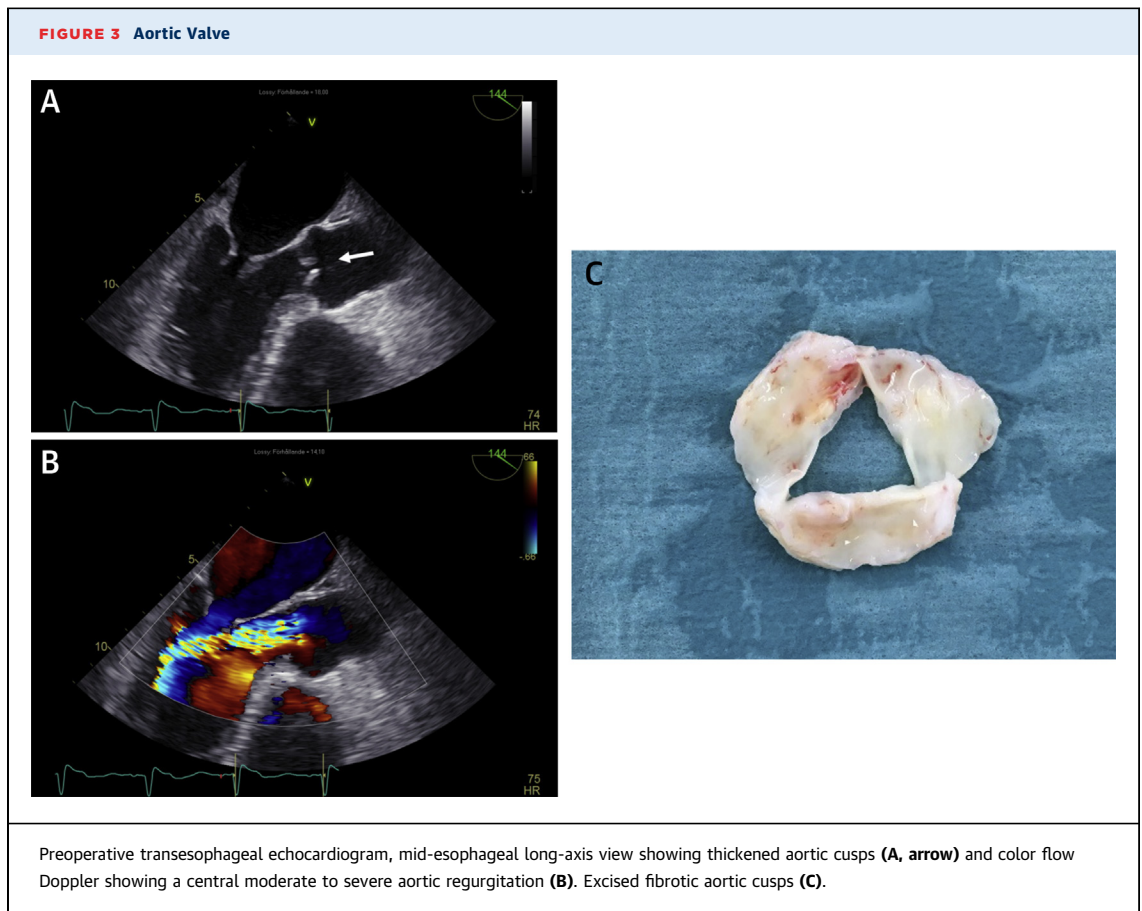


Preoperative transthoracic echocardiogram, parasternal short-axis view, showing thickened tricuspid leaflets (A, arrow). Color flow and continuous wave Doppler showing severe tricuspid regurgitation (B, C).

FIGURE 2 Pulmonary Valve



Preoperative transthoracic echocardiogram, parasternal short-axis view, color flow, and pulsed Doppler showing moderate pulmonary regurgitation (A, B). Excised fibrotic pulmonary cusps (C).



daily. Echocardiography showed all 4 valves were functioning well, with normal postoperative gradients and no paravalvular leakage. Further oncological follow-up demonstrated no signs of carcinoid tumor progression. Laboratory analyses showed concentrations of: creatinine, 144 $\mu\text{mol/l}$; NT-proBNP, 561 ng/l; (U) 5-HIAA, 78 $\mu\text{mol/day}$; and chromogranin A, 13 nmol/l.

DISCUSSION

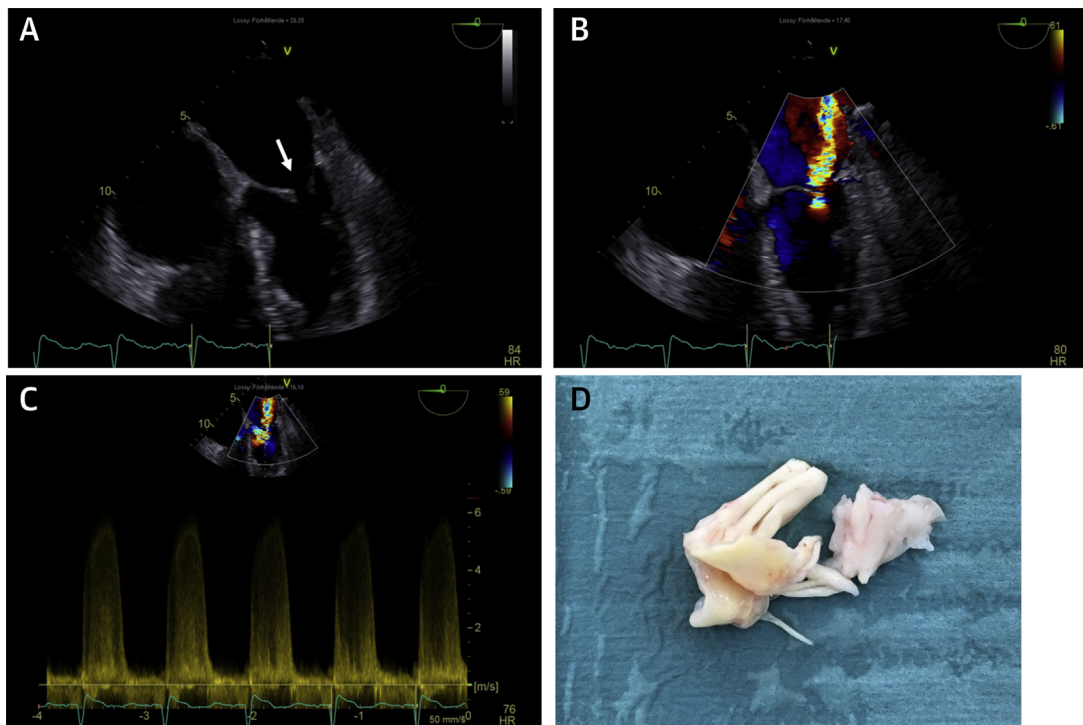
Neuroendocrine tumors are rare, slow-growing malignancies (2.5 to 5 cases per 100,000 persons), most frequently arising in the gastrointestinal tract and metastasizing to the liver. Patients may experience carcinoid syndrome with episodes of flushing and diarrhea. CaHD is a valvular complication of metastatic NET, with progressive development of plaque-like fibrous thickening of the right-sided valves, believed to be caused by high levels of circulating serotonin and related vasoactive metabolites from the hepatic metastases. The right-sided valve components become stiff and retracted, eventually leading to massive tricuspid regurgitation, whereas the

pulmonary valve may show a combination of stenosis and regurgitation. Approximately 20% to 50% of patients with carcinoid syndrome develop CaHD, causing progressive right heart failure and carrying a dismal prognosis with a 3-year survival of 31%, compared with 68% in patients with NETs but no CaHD (1).

Valve replacement in patients with severe CaHD has been shown to reduce heart failure symptoms, increase functional capacity, and allow for more aggressive oncological treatment. In the largest reported cohort of 240 CaHD patients who underwent surgery at the Mayo Clinic (2), early surgical mortality was reduced from 29% in the 1990s to 5% in the recent era. Functionally, 64% of patients were in NYHA functional classes III to IV preoperatively, whereas 85% were in NYHA functional classes I to II postoperatively. Long-term survival was 48% at 3 years and 34% at 5 years, with most patients dying from progressive tumor burden. Bioprosthetic valves were used in 85% of patients with very few patients needing reintervention due to thrombosis or prosthesis degeneration later on.

In 5% to 10% of patients with CaHD, the aortic and mitral valves are involved, in addition to the

FIGURE 4 Mitral Valve



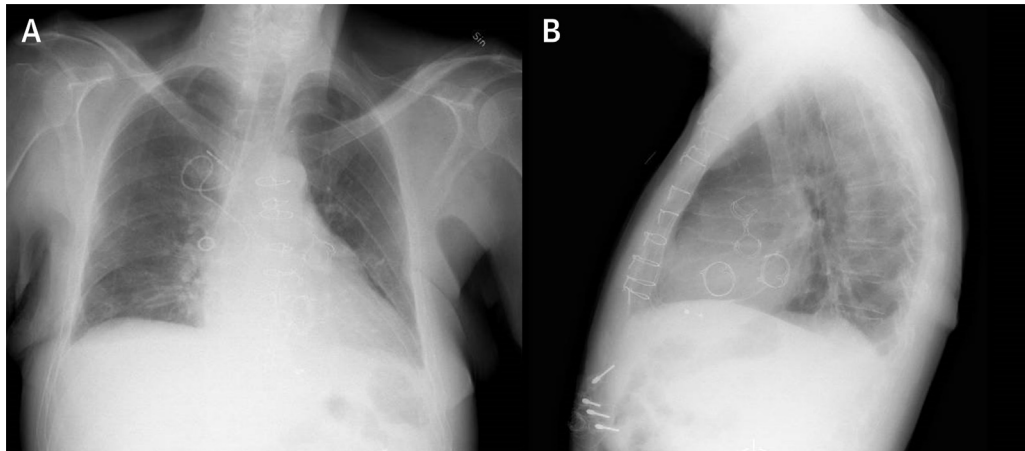
Preoperative transesophageal echocardiogram, mid-esophageal 4-chamber view, showing thickened mitral valve leaflets (**A**, arrow) and color flow and continuous wave Doppler showing severe mitral regurgitation (**B**, **C**). Excised fibrotic anterior leaflet and parts of posterior leaflet with fused chordae (**D**).

right-sided valves (3). It has been speculated that vasoactive hormones are inactivated in the lung circulation, thereby sparing the left-sided valves, although they may be affected by a right-to-left intracardiac shunt such as a PFO. However, in the Mayo series (2), 66% of patients with left-sided involvement did not have a PFO. Correspondingly, in the present patient, there was no intracardiac shunt found either on echocardiography or intraoperatively, although an agitated saline contrast study was not performed, as recommended by some authors (3). Furthermore, there were no signs of other causative factors of left-sided CaHD, such as a bronchial carcinoid tumor or extremely high levels of circulating serotonin. In a study by Bhattacharyya et al. (4), similar serotonin levels were demonstrated in both ventricles in patients with CaHD, indicating that individual heart valves may have a variable susceptibility to developing dysfunction not solely related to serotonin levels. In the Mayo study (2), left-sided valves were operated on in 16% of patients; the need for left-sided valve surgery was not related to overall mortality and

was considered safe and recommended if clinically indicated.

Quadruple valve surgery in CaHD has previously been described in only a few case series (5-7). Castillo et al. (5) reported a successful isolated case of a patient who had bioprosthetic replacement of the right-sided valves but repair of the aortic and mitral valves. Seven patients were reported from the Mayo Clinic (6), almost all of whom had mechanical valves implanted. To the best of the present authors' knowledge, quadruple valve replacement with all bioprosthetic valves has been reported in only 1 previous patient (7). Conventionally, the present authors use bioprosthetic valves in CaHD patients who have limited life expectancy and may not manage warfarin therapy well due to hepatic tumor burden. There is a concern for recurrent carcinoid involvement in bioprostheses, although this is supposedly unusual (2). If present, such problems may be treated by transcatheter techniques.

Intraoperative management to prevent potentially dangerous effects of the carcinoid disease is important, as anesthesia, surgery, and various medications

FIGURE 5 Chest Radiograph

Chest radiograph obtained 10 days postoperatively with normal findings. Frontal (A) and lateral (B) views.

may trigger the release of vasoactive hormones. This may lead to a carcinoid crisis with bronchospasm, hypotension, and hemodynamic instability. In our patient, there were no signs of this complication, following our policy to administer intravenous octreotide infusions of 50 to 100 $\mu\text{g}/\text{h}$ from anesthesia induction throughout surgery and then 50 $\mu\text{g}/\text{h}$ postoperatively for several days in collaboration with endocrine oncologists. During follow-up, the present patient had no detectable radiological tumor progression and showed a decline in (U) 5-HIAA and chromogranin A concentrations, possibly related to an increase in long-acting octreotide given postoperatively. In the present authors' experience, however, it is not uncommon to see a decline in these parameters with the reduction of right heart failure and improvement in hemodynamic status after surgery. These authors do not believe it is related to tumor reduction. For anticoagulation, LMW heparin is usually applied subcutaneously for 3 months postoperatively, but in the current case with 4 valves,

the authors did not dare refrain from warfarin therapy. This had to be changed to LMW heparin, however, due to the spontaneous psoas muscle hemorrhage.

CONCLUSIONS

CaHD is a rare condition that may affect all 4 valves simultaneously. Presence of an intracardiac shunt is not a prerequisite for left-sided valve involvement. Even in extensive CaHD, some patients can tolerate and benefit from quadruple valve replacement. Multidisciplinary collaboration is required for optimal patient selection, timing of surgery, perioperative management, and postoperative care.

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KEY WORDS carcinoid heart disease, cardiac surgery, valve replacement

APPENDIX For supplemental videos, please see the online version of this paper.